REMARKS

Claims 1-157 were in this case. Claims 4-16, 24-27, 31-40, 43-58, 61, 63, 65, 67, 69, 70, 75-80, 87-89, 93, 96-139 and 156 have been withdrawn from consideration as directed to a non-elected invention. This response cancels claims 1-16, 18-19, 24-27, 31-40, 44-58, 62, 67, 75-81, 85-88 and 93-139 without prejudice. Certain of these claims were withdrawn as directed to a non-elected invention and others where considered redundant in view of other claim amendments. Claims 17, 28, 41, 59, 64, 66, 68, 71-74, 82, 91, 140, 145, 146, 154, and 157 have been amended. New claims 158 -164 have been added. New claim 158 depends from claim 144. New claim 159 is independent and new claims 160 and 161 depend from claim 159. New claims 162-164 depend from claim 28. These new claims all read on the elected invention. Claims 17, 20-23, 28-30, 41, 42, 59, 60, 64, 66, 68, 71-74, 82-84, 90-92, 140-155, 157, and 158-164 are currently under consideration in this case. Claims 43, 61, 63, 65, 69, 70, 89 and 156 are currently withdrawn from prosecution, but have been retained by Applicant for possible rejoinder.

Information Disclosure Statement

The undersigned thanks the Examiner for providing initialed copies of the 1449 forms submitted.

Error in the Office Action

On the PTOL-326 form attached to the Office Action, claims 145-147 are said to be rejected. These claims are stated to be allowable over the prior art on page 24 of the Office action. Further, these claims have not been rejected under 35 U.S.C. 112. These claims are thus believed to only be objected to and Applicant assumes that these claims would be allowable if rewritten in independent form. In this response, these claims have been amended to depend from amended claim 144. This amendment should not affect patentability of the subject matter of these specific claims.

Claim Amendments

Claim 28 has been amended to make it independent carrying all of the limitations of claim 1 from which it depended. Claim 28 has also been amended to recite that the molecular scaffold is "a ring-opening metathesis polymerization scaffold' and that "one or more of the signal recognition elements is an N-formyl peptide or an N-acyl peptide."

This further amendment is supported in original claims 66 and 81. Claims 66 and 81 have now been canceled as redundant. The addition of N-acyl peptide is supported in the specification at page 9, lines 16-17 which indicates that both N-formyl and N-acyl peptides act as chemoattractants. N-acyl peptides are further supported at page 15, lines 22-23, where it is stated that "receptors for N-formylated peptides may also bind to other derivatized peptides such as N-acyl-peptides." Note that claim 150 has been amended to depend from claim 28 and is directed to the use of certain ROMP multivalent ligands where one or more of the signal recognition elements are N-formyl peptides.

Claims 17, 41, 59, 63-66, 68, 71-74, 82, 140 and 157 have been amended to depend from claim 28.

Claim 82 has also been amended to recite that "a plurality of R^1 or R^2 in the ligand are $-L^1$-SRE" which is consistent with the language of claim 28 which states that the multivalent ligand contains a plurality of SRE groups.

Claim 91 has been amended to delete an extraneous repetition of "(F, Br, Cl, I)."

Claim 144 has been made independent incorporating the limitation of claim 1. Claim 144 was dependent upon claim 91 which ultimately depended from claim 1. The dependency of claim 144 on claim 91 was incorrect. Claim 144 should have depended directly from claim 82. Both claims 82 and 91 depended from claim 1, so to make claim 144 independent the limitations of claim 1 were introduced. Claim 144 has also been amended to incorporate the limitation of original claim 66 to recite that one or more of the SRE groups is an N- formyl peptide. Claim 144 has also been amended to recite that the multivalent ligand contains a plurality of SRE groups which is consistent with the

language of claim 1. Claim 144 as amended incorporates the limitations of original claim 144 as well as claim 66.

Claim 141 has been amended to depend from claim 144.

Claim 148 has been amended to recite that a plurality of the R^1 and R^2 groups in the ligand are $-L^3$-SRE which is consistent with the language of claim 28 from which claim 148 depends.

Claims 154 and 155 have been amended to correct minor typographic errors.

Claims 1-16, 18-19, 24-27, 31-40, 44-58, 62, 66, 67, 75-81, 83-88, 93-139, and 149 have been canceled.

Claim 150 has been amended to depend from claim 28 and to recite that one or more of the signal recognition elements is an N-formyl peptide. This amendment is supported

New claims 158-164 have been added.

New claim 158 depends from claim 144 and recites that the N-formyl peptide has the structure identified as fMLP in the specification at page 63 in Scheme 2.

New claim 159 is similar in scope to claim 144 as amended except that the structure of the multivalent ligand has been broadened to encompass certain multivalent ligands in which the double bonds of the backbone are reacted to incorporate Z groups. This amendment is supported in the specification in the broad structure on page 21 (top) and the definition of the BB group on page 22 at about line10. The use of such multivalent ligands where SRE are N-formyl peptides is supported in Scheme 2, for example, in structure 23.

New claim 160 depends from claim 159 and recites that the N-formyl peptide has the structure identified as fMLP in the specification at page 63 in Scheme 2. New claim 161 depends from claim 159 and recites that z is OH. These new claims are supported on page 62 of the specification in Scheme 2.

New claims 162-164 depend from claim 28 and are supported by original claims 107-109 which were directed to multivalent ligands and by original claim 150 wherein SRE are defined as N-formyl peptides.

Claims 63, 69, 70 and 156 are formally withdrawn from consideration. These claims have, however, been amended to depend from claim 28.

Applicants note that all of claims 43, 61, 63, 65, 69, 70, 89 and 156 which are formally withdrawn now depend from claim 28 due to the claim amendments made.

In summary, all of claims 17, 20-23, 29, 30, 41-43, 59-61, 64, 68, 71-74, 82, 90-92, 140, 142, 143, 148, 151-155, 157 and 162-164 depend from claim 28 which has been amended to make it independent and to recite that the multivalent ligand contains a molecular scaffold that is a ring-opening metathesis polymerization scaffold and that one or more of the signal recognition elements are N-formyl peptides.

Claim 144 has been amended to be independent incorporating the method limitations of claim 1 and further incorporating the limitation of original claim 66 that at least one SRE of the multivalent ligand is an N-formyl peptide. Claims 141, 145-147 and new claim 158 now depend from independent claim 144.

New independent claim 159 has been added and new claims 160 and 161 depend therefrom. Claim 159 is similar in scope to claim 144, but allows the backbone of the molecular scaffold to be substituted with certain groups.

The amendments do not add new matter to the claims.

The Remaining Withdrawn Claims

Claims 43, 61, 63, 65, 69, 70, 89 and 156 are formally withdrawn from consideration as directed to non-elected inventions. All of these claims now depend from claim 28. Claims 61 and 89 are directed to the use of multivalent ligands containing in addition to other groups a label or reporter group. Applicant respectfully request rejoinder of these claims once a generic claim is found allowable. Claims 63 is directed to a method employing multivalent ligands in which the recognition element is a saccharide or derivatized saccharide and claim 65 is directed to a method wherein a signal recognition element of the multivalent ligand is a protein. Again Applicant respectfully requests rejoinder of these claims on allowance of a generic claim. Claim 156 is directed to methods

practiced in vivo or ex vivo again Applicant requests rejoinder in the event of allowance of a generic claim.

Applicant requests reconsideration of the withdrawal of claims 69 and 70. It is unclear why these claims are considered withdrawn in view of the inclusion of claims 68, 72 and 73 in the group of claims under consideration. Claim 68 is directed to the use of a multivalent ligand having a defined number of signal recognition elements. Claim 69 and 70 are directed to methods employing multivalent ligands with specific numbers of signal recognition elements.

The Rejections

35 U.S.C 112, first paragraph

Claims 1-3, 17-23, 28-30, 41, 42, 59, 60, 62, 64, 66, 68, 71-74, 81-86, 90-92, 94, 95, 140-143, 151-155 and 157 have been rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. Applicants respectfully traverse this rejection with respect to the claims as amended

Claims 1-3, 18-19, 62, 81, 85, 86, 94, and 95 have been canceled. Claim 28 has been made independent and carries the limitations of claim1, claim 81 and claim 66. All of claims 17, 20-23, 29, 30, 41, 42, 59, 60, 64, 66, 64, 71-74, 82-84, 90-92, 140, 142-143, 151-155 and 157 now depend from amended claim 28. New claims 162-164 depend from claim 28. All of these claims are now directed to a method for inducing the release of an intracellular signal by a cell in a biological system additionally require that the molecular scaffold of the multivalent ligand is a ring-opening metathesis polymerization scaffold and further require that one or more of the signal recognition elements is an N-formyl peptide or an N-acyl peptide.

The Office Action states:

> The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a

rejection for lack of written description. The claims are broadly drawn to methods for inducing a biological response in a biological system by introducing a multivalent ligand comprising a plurality of signal recognition elements (see claim 1). The specification (at p. 27, lines 18-20) contemplates, methods wherein the multivalent ligands of the instant invention are useful "for controlling or modulating the effect of chemical signals in a biological system." The specification, at p. 27, lines 19-23, states that the instant disclosure exemplifies application of "multivalent ligands to bacterial and eukaryotic chemotaxis, to migration of leukocytes (particularly neutrophils), to immune responses of B-cells and T- cells, to cell aggregation, and to signaling of apoptosis." Actual working embodiments (specification at p. 45, line 21-p. 50, line 27 and pp. 60-64, Scheme 1-Scheme 5) involve saccharide ligands for chemotaxis in E. coli and concanavalin A-mediated agglutination in Jurkat T cells and erythrocytes and PC12 cell cytotoxicity experiments. Vas-Cath Inc. v. Mahurkar, 19 USPQ 2d 1111, 1117, states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." The instant specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116). To provide adequate written description and to provide evidence of possession of a claimed genus, the specification must provide a representative number of species. When there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus and describe sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and / or chemical properties, functional characteristics, structure / function correlation, methods of making the claimed product, and combinations thereof. The broad genus of methods inducing a biological response using multivalent ligands admits to substantial variation that would include virtually any biological response. The specification exemplifies five general categories (chemotaxis, leukocyte migration, immune response, cell aggregation and apoptosis) and provides working examples of as few as two multivalent ligands (a saccharide and concanavalin A). The examiner respectfully submits that the examples are not so comprehensive as to be representative of the full scope of the claimed genus. Furthermore, the rejected claims recite little molecular structure or identity for the receptors, signal recognition-elements, or molecular scaffold. Accordingly, the specification does not provide adequate written description of the claimed genus of

> methods inducing biological responses, comprising receptors, ligands, and molecular scaffolds. The skilled artisan cannot envision the detailed chemical structure of the encompassed genus of all multivalent ligands that bind to any receptor to induce any biological response, and given the few actual examples provided and the unpredictability of the ligand-receptor and medicinal drug art, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of making and using multivalent ligands. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The multivalent ligands themselves are required. See Fiers v. Revel, 25 USPQ2d 1601 at 1606 (CAFC 1993) and Amqen Inc. v. Chuqai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481, at 1483 (finding claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class, where the specification provided only the bovine sequence). Therefore, only the methods comprising specific multivalent ligands that bind to cellular receptors to induce chemotaxis or agglutination, as taught by the instant specification, but not the full breadth of the claim, meets the written description provision of 35 U.S.C. § 112, first paragraph. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. § 112 is severable from its enablement provision (see page 1115).

The amended claims are directed to a method for inducing release of an intracellular signal by a cell by contacting the cell with a ROMP ligand which carries at least one N-formyl peptide or one N-acyl peptide. On page 40 of the specification, it is noted that N-formyl peptides function as chemoattractants and that certain cells release intercellular signals that affect responses in other cells and that this is particularly observed in immune systems cells. It is specifically stated that multivalent ligands of the invention can be used to enhance the response of neutrophils to chemoattractants and enhance immune system clearance of infectious agents. Further Scheme 2 illustrates an exemplary N-formyl peptide **20** and an exemplary SRE for that N-formyl peptide **21** for use in multivalent ligands that modulate neutrophil migration. It is stated that these signal groups (SREs) can be covalently or noncovalently bonded to ROMP scaffolds such as those illustrated in Scheme 2 (**22** and **23**). Additionally,

Scheme 3 provides exemplary linkers that can be employed in multivalent ligands carrying N- formyl-peptides.

Additional description of the use of multivalent ligands carrying N-formyl peptides and N-acyl peptides is found on page 9 of the specification where it is stated that multivalent ligands of the invention can be used to modulate the response of leukocytes, including neutrophils, to chemoattractants (including derivatized peptides, such as N-formyl peptides and N-acyl peptides) and can modulate the activation and deactivation of B-cells and/or T-cells.

Further description of the application of multivalent ligands carrying N-formyl peptides or N-acyl peptides is found on pages 15-16, where it is stated that any ligand (which may include species that act as agonist or antagonists of receptor function) of a N-formylated peptide receptor may be employed for applications related to that receptor which is said to include N-acyl peptides. It is also stated that: "A chemoattractant may induce biological responses in addition to migration or chemotaxis. For example, in various types of leukocytes, chemoattractants can induce the release of toxic species or the release of inflammatory cytokines, transcription factors and other chemical species which, in turn, function as chemical signals for other cells."

Applicant describes both N-formyl peptides and N-acyl peptides in the specification as types of chemoattractant and teaches that multivalent ligands carrying N-formyl peptides or N-acyl peptides can induce signal release from cells. Additionally, the specification provides examples of N-formyl peptides, and examples of structures of ROMP multivalent ligands that carry N-formyl peptides that are stated to function as chemoattractants and for the release of signal from cells. These statements should be considered to be true, unless there is reason to doubt the objective truth of the statements (see In re Marzocchi, 169 USPQ 367, in reference to the enablement requirement of 35 U.S.C. 112, first paragraph). While the enablement requirement is severable from the written description requirement, facts which support enablement can clearly be used to support sufficiency of the written description. If Applicant's statements are considered reasonable to support enablement, they should be considered

sufficiently reasonable to also support written description. Applicants submit that it should be considered that these statements regarding functionality would be believed by one of ordinary skill in the art to be true, unless there is some reason given on the record why the skill artisan would doubt these statements. No reason has been given on the record why the skilled artisan would doubt Applicant's statements regarding the functionality of the ROMP multivalent ligands. Thus, the skilled artisan believing these statements of functionality would consider that Applicants were in possession of the invention as now claimed with respect to induction of signals employing multivalent ligands having a ROMP polymer backbone structure and carrying one or more N-formyl peptides or N-acyl peptides.

Further, one of ordinary skill in the art in view of the descriptions in the specification and his or her knowledge of the art would appreciate that various ROMP backbone structures such as those described in formulas on pages 21, 22, and 25-28 can be prepared employing methods described and exemplified in the specification in view of methods that are well-known in the art. Thus, Applicants description via the structures illustrated in the specification provides a sufficiently detailed description such that one of ordinary skill in the art, who is aware of the art concerning the structure and synthesis of ROMP polymers, would understand that Applicant had possession of the invention as claimed with respect to ROMP polymers.

Additionally, one of ordinary skill in the art in view of the descriptions in the specification concerning the applications of N-formyl peptides and N-acyl peptides including the examples teaching the synthesis of exemplary N-formyl peptides and in view of his or her knowledge of the art would appreciate that various N-formyl peptides and N-acyl peptides could be substituted for those specifically exemplified and would consider that Applicant had possession of the invention as claimed with respect to N-formyl and N-acyl peptides.

With respect to the basis of this rejection given in the Office Action, the claims are now directed to a more specific application, i.e., to the induction of release of a signal employing more specific multivalent ligands, i.e., those having

a ROMP polymer backbone structure and carrying one or more N-formyl or N-acyl peptides. The specification provides examples of the application, i.e., signal release from neutrophils and other immune system cells, and provides significant structural detail for ROMP polymers employed as multivalent ligands in formulas and examples. The specification also provides examples of N-formyl peptides and states that N-acyl peptides will exhibit similar function. Applicants submit that the formulas, structures, examples and description regarding synthesis of the ROMP-based multivalent ligands containing N-formyl and N-acyl peptides provide a written description that is sufficient in view of what is known in the art about such polymers and derivatized peptides that the skilled artisan would consider that Applicant was in possession of the invention as now claimed at the time the application was filed.

In view of the amendment of the claims and all of the forgoing arguments, it is submitted that the specification provides a sufficient written description for the claims as amended.

Claims 144-150 were not rejected for lack of written description. Claim 141 and new claim 158 depend from claim 144 and as a result are believed to be considered to meet the written description requirement.

New claims 159-161 have been added. Claim 159 is similar is scope to claim 144 except that the double bonds of the polymer backbone of the ROMP polymer are reduced to add specific Z groups as are specified in the formula on page 21. A description of the reduction of the double bonds of the ROMP polymer are given on page 20 beginning at line 24 and in Scheme 6 which provides two examples of reduced backbones of the structures of claim 159. Additionally, it is indicates on page 39, starting at line 26, and as illustrated in Scheme 2 that multivalent ligands having double bonds and reduced double bonds in the polymer backbone carrying N-formyl peptides can be employed in the invention. It is believed that claims 159-161 meet the written description requirement.

Prior Art Rejections

35 U.S.C 102

Claims 1, 2, 3, 17, 19, 21, 22, 30, 59, 60, 62, 68, 81, 82, 85, 86, 90, 91, 95, 142, 143, 144, are rejected under 35 U.S.C. § 102(a) as being anticipated by Gordon et al., (Chemistry K Biology, vol. 7:9-16, 2000). The Office Action states that "(t)his rejection maintains the reasons of record set forth in the previous Office action, mailed 6/3/2004, and is extended to claims 2, 3, 17, 19, 21, 22, 30, 59, 60, 62, 68, 91, 95, 142, 143 and 144. Claims 1-3, 19, 62, 81, 85, 86, and 95 have been canceled obviating the rejection with respect to these claims. Claims 17, 21, 22, 30, 59, 60, 68, 82, 90, 91, 142, and 143 all now depend ultimately from claim 28 which was not rejected over Gordon et al. Claim 144 has been amended to include the limitation of original claim 66 which is not rejected over Gordon et al. It is believed that the amendment of the claims obviates this rejection.

Applicants reiterate the arguments presented in the previous response that the Gordon reference while teaching that certain multivalent ligands bind to L-selectin, does not **demonstrate** that this binding causes any biological response. Gordon does not show that binding of a multivalent ligand to L-selecting "recruits white cells to sites of tissue damage." No such experiments were reported. The Gordon reference provides very useful methods of synthesis for the preparation of multivalent ligands. The Gordon reference employs ligand binding with a fluorescent reporter to visualize cells and suggests on page 14, column 1, lines 3-5 that the ligands produced using the methods disclosed "will facilitate a wide range of mechanistic investigation of cell surface-ligand binding events." Thus, at most, the Gordon reference suggests that the multivalent ligands disclosed should be used to investigate biological effects.

Claims 1-3, 17, 18, 19, 20-23, 28-30, 41, 42, 59, 60, 62, 64, 68, 71-74, 82, 83, 90-92, 94, 95 140-143, 151, 154, 155, 157 are rejected under 35 U.S.C. § 102(b) as being anticipated by Whitesides et al., WO 98/46270 (reference 4, IDS filed 10/10/2002). This rejection maintains the reasons of record set forth in the previous Office action, mailed 6/3/2004, and has been extended to claims 18, 19,

82, 83, 90-92, 94, 95, and 141. Applicants respectfully traverse this rejection in view of the amendment of the claims.

Claims 1-3, and 62 have been canceled. As noted above, many of the claims remaining in this case have been amended to depend from amended claim 28. Claim 28 as amended recites the limitations of claims 66 and 81 that the molecular scaffold of the multivalent ligand is a ring-opening metathesis polymerization scaffold and that one or more of the signal recognition elements is an N-formyl peptide. Claims 66 and 81 are not rejected as anticipated by Whitesides. Whitesides does not teach any multivalent ligand having a molecular scaffold that is a ring-opening metathesis polymerization scaffold. Neither, does Whitesides teach or suggest N-formyl or N-Acyl peptides as ligands in a polyvalent presenter. Thus, claim 28 as amended to include these limitations is also not anticipated by Whitesides. All of claims 17, 20-23, 29, 30, 41, 42, 59, 60, 64, 68, 71-74, 82, 83, 90-92, 94, 95, 140, 142, 143, 151, 154, 155, and 157 depend from amended claim 28. Claim 141 has been amended to depend from claim 144 which is not rejected as anticipated by Whitesides et al. This rejection should be withdrawn with respect to all of the listed claims in view of the amendment.

Claims 1, 81, 82, 83, 85, and 90 are rejected under 35 U.S.C. g 102(e) as being anticipated by Kiessling et al., US 6,291,616, (reference 1, IDS filed 10/10/2002). Claims 1, 81, and 85 have been canceled obviating the rejection with respect to these claims. Claims 82, 83 and 90 now depend ultimately from claim 28 which is not rejected over US patent 6,291,616. It is believed that in view of the amendments to the claims that claims 82, 83 and 90 should be considered allowable over the cited reference.

Applicants reiterate the arguments previously presented. US 6,291,616. teaches "methods of preparing a telechelic polymer (mono- or bi-telechelic) that use a ruthenium or osmium carbene catalyst and a capping agent, at least one of which is functionalized" (See Abstract). There is no **demonstration** in this reference that any multivalent ligand induces a biological response as required by Applicants' claims herein. In particular, the patent does not teach that a

multivalent ligand as now claimed induces the release of an intracellular signal by a cell in a biological system. Thus, the cited art does not teach Applicants' claimed method and does not anticipate Applicants' claims. This rejection should be withdrawn.

Claims 1-3, 59, 60, 62, 64, 68, 74, 81, 82, 83, 90, 91, 92, 144, and 157 are rejected under 35 U.S.C. 102(a) as being anticipated by Arimoto et al., Chem. Commun., July 1999, Vol. 15, 1361-1362, (IDS filed 10/10/2002, ref. 11). Claims 1-3, 62, and 81 have been canceled obviating the rejection of these claims. Claims 59, 60, 64, 68, 74, 81, 82, 83, 90-92, and 157 have been amended to ultimately depend from claim 28 which is not rejected over Arimoto et al. Claim 144 has been amended to include the limitation of claim 66 which is not rejected over Arimoto et al. It is believed that in view of the amendment of the claims that this rejection is obviated and should be withdrawn.

The Office Action states:

> The claims are drawn to methods for inducing a biological response in a biological system comprising one or more receptors wherein a multivalent ligand comprising a plurality of signal recognition elements bonded to molecular scaffold and wherein the signal recognition elements are recognized by at least one of the receptors, and variations thereof. Arimoto et al., throughout the publication and Figures and Scheme 1, teach methods for inducing antibacterial activity by introducing a multivalent ligand comprising a plurality of vancomycin residues, reading on signal recognition elements bonded to a ROMP-derived molecular scaffold of the formula of claim 82, that binds to D-Ala-D-Ala residue of the pentapeptide terminal of biosynthetic intermediates, which, absent evidence to the contrary, reads on a receptor of bacteria. Arimoto teaches at Scheme 1, polymers of the general formula of claims 82, 91 (where m=0 and n=2 or more) and 144.

Arimoto et al. teaches the use of a polymer containing multiple vancomycin residues to "strengthen the association" of the binding of vancomycin with the D-Ala-D-Ala residue of the pentapeptide terminal of a bacterial biosynthetic intermediate to interfere with bacterial biosynthesis and enhance antibacterial activity (Arimoto et al. page 1361, column 1, third paragraph). Arimoto et al. does not demonstrate inducing the release of an

intracellular signal by a cell in a biological system as is required by claim 28. This rejection should be withdrawn with respect to all of the claims remaining in this case.

Claims 1-3, 17, 28, 29, 59, 60, 62, 64, 68, 71-74, 81, 82, 83, 90, 91, 142, 144, 152 and 157 are rejected under 35 U.S.C. 102(b) as being anticipated by Kanai et al., J. Am. Chem. Soc, 1997, Vol. 119 (41), pp. 1361-1362, (IDS filed 10/10/2002, ref. 45). Applicants respectfully traverse this rejection with respect to the claims as amended. Claims 1-3, 62, and 81 have been canceled. Claims 17, 29, 59, 60, 64, 68, 71-74, 81, 82, 83, 90, 91, 142, 152 and 157 all now depend from claim 28 and carry its limitations. Claim 28 has been amended to include the limitations of both of claims 66 and 81. Claim 144 has been amended to include the limitations of claim 66. Claim 66 is not rejected over Kanai et al. It is believed that the amendment of claims 28 and 144 obviates this rejection with respect to all of the listed claims.

35 U.S.C. 103

Claims 1-3, 17, 18, 19, 20-23, 28-30, 41, 42, 59, 60, 62, 64, 68, 71-74, 81, 82, 83, 90-92, 94, 95, 140-143, 144, 148, 149, 151, 154, 155, 157 are rejected under 35 U.S.C. 103(a) as being unpatentable over Whitesides et al., WO 98/46270 (reference 4, IDS filed 10/10/2002); and Arimoto et al., Chem. Commun., July 1999, Vol. 15, 1361-1362, (IDS filed 10/10/2002, ref. 11). Claims 1-3, 62 and 81 have been canceled. Claim 144 has been amended to incorporate the limitation of claim 66 which is not rejected over this combination of references. Claim 141 now depends from amended claim 144. The rejection of claims 144 and 141 should be withdrawn in view of this amendment.

The remaining rejected claims have been made dependent upon amended claim 28. Because claim 66 is not included in this rejection, amended claim 28 is believed to be patentable over the combination of references cited. The amendment of the claims is believed to obviate this rejection.

Claims 66, 84, and 150 are rejected under 35 U.S.C. 103(a) as being unpatentable over Whitesides et al., WO 98/46270 (reference 4, IDS filed

10/10/2002), Arimoto et al., Chem. Commun., July 1999, Vol. 15, 1361-1362, (IDS filed 10/10/2002, ref. 11) as applied to claims 1-3, 17, 18, 19, 20-23, 28-30, 41, 42, 59, 60, 62, 64, 68, 71- 74, 81, 82, 83, 90-92, 94, 95, 140-143, 144, 148, 149, 151, 154, 155, 157 above, and further in view of Painter et al., Journal of Cell Biology, 1987, vol. 105, pp. 2959-2971 (previously cited by examiner). Claims 66 and 150 have been canceled. However, claims 28 and 144 from which all remaining claims depend carry the limitation of claim 66. Applicants respectfully traverse this rejection with respect to the claims as amended.

The Office Action states:

> The claims are drawn to methods for inducing a biological response in a biological system comprising one or more receptors wherein a multivalent ligand comprising a plurality of signal recognition elements wherein the signal recognition elements are recognized by at least one of the receptors and wherein the signal recognition elements are bonded to molecular scaffold, and wherein the signal recognition element is a derivatized peptide and is an N-formylated peptide, as in claims 66, 84 and 150. Whitesides et al., teach methods for inducing a biological response using multivalent ligands, including ligands where the signal recognition element is a peptide, as presented above. Arimoto et al., teach methods for inducing a biological response by multivalent ligands having the structure as formulated as in claim 144, as presented above. Neither of Whitesides et al. or Arimoto et al., as above, teach methods for inducing a biological response by multivalent ligands, wherein the signal recognition element is a derivatized peptide and is an N-formylated peptide. Painter et al., teach a derivatized peptide that is an N-formylated peptide that is a ligand that binds to a glycoprotein receptor and acts as a recognition element to stimulate chemotaxis of human neutrophils. It would have been prima facie obvious for one of ordinary skill in the art at the time of the invention to combine methods of comprising inducing biological response by multivalent ligands that bind to receptors, wherein such methods comprise ligands with derivatized or N-formylated peptides. One of ordinary skill in the art would have been motivated to use methods comprising derivatized or N-formylated peptides in multivalent ligands in order to stimulate chemotaxis of human neutrophils, as taught by Painter et al. One of ordinary skill in the art would have had a reasonable expectation of success, because N-formylation of peptides was long known in the art, as was the formylated peptide induction of neutrophil chemotaxis.

The disclosure of Whitesides et al. provides much speculation about the polyvalently presenting active moieties (so-called polyvalent presenters). Among the many possible active moieties discussed in the Whitesides disclosure, there is no specific disclosure of multivalent ligands containing N-formyl or N-acyl peptides and no specific disclosure of the use of such ligands for inducing the release of a signal from a cell. It is noteworthy, in the listing of polyvalent cell-cell interactions in Table 2 (which refers to neutrophils), in the listing of ligands and receptors of Table 3 there is no mention of N-formyl peptides or N-acyl peptides, in the additional listings in the remaining Tables there is no mention of N-formyl peptides or N-acyl peptides. There is a reference to bacterial chemotaxis in Table 7 which refers to dimerization of bacterial receptor by aspartate where it is noted that the mechanism of this interaction is "possibly non-polyvalent." The specific teaching of the Whitesides et al. reference is the use of poly(acrylic acid) for presenting sialosides to inhibit hemagglutination, an RGD (a peptide)-polyaspartic acid to screen for fibrinogen binding to platelets, poly(acrylic acid) and poly(butadiene-co-maleic anhydride) for presenting galactosides to prevent adhesion of ricins; poly(acrylic acid) presenting n-acetylglusoamine for induction of acrosomal exocytosis. There is no specific enabling teaching of the use of any polymer presenting N-formyl or N-acetyl peptides.

Throughout the Whiteside et al. disclosure there is a discussion of polyvalency and polyvalent interactions. (see Background of the Invention). The underlying theme of the disclosure is that benefit is to be obtained by presenting a polymer containing multiple copies of an active species. In all of the discussion of such polyvalency and polyvalent interactions, there is no teaching or suggestion that N-formyl peptides or N-acyl peptides presented in a polyvalent presenter would provide any benefit. More specifically, there is no teaching or suggestion in Whitesides et al. that any multivalent ligand containing N-formyl or N-acyl peptides would induce any biological response or more specifically would induce the release of an intracellular signal on interaction with a cell.

Arimoto et al. teaches a multivalent ROMP polymer carrying vancomycin (a peptide antibiotic). Vancomycin is known to function by binding to and

inhibiting an intermediate of bacterial cell wall biosynthesis. It is stated that "since this binding interferes with bacterial peptidoglycan biosynthesis, it is widely believed that strengthening the association could enhance antibacterial activity." Arimoto et al. do not teach or suggest that anything about the release of intracellular signals. More specifically there is no teaching or suggestion that any strengthening of the binding interaction by use of a polyvalent species would have any beneficial effect on the induction of intracellular signal by N-formyl or N-acyl peptides.

Painter et al. is characterized as teaching a derivatized peptide that is an N-formylated peptide that is a ligand that binds to a glycoprotein receptor and acts as a recognition element to stimulate chemotaxis of human neutrophils. However, there is no teaching or suggestion in Painter et al. that any polymer containing an N-formyl peptide would retain the function of the N-formyl peptide to stimulate chemotaxis of human neutrophils and further there is no teaching or suggestion that any benefit could be obtained by presenting an N-formyl peptide to the neutrophil in a polyvalent manner.

Thus, no reasoning has been presented on the record substantiating that one of ordinary skill in the art would have been motivated to prepare a ROMP polymer to present a plurality of signal recognition elements including one or more N-formyl peptides or N-acyl peptides for signal induction in a cell. There is no such teaching or suggestion in Whitesides et al. or Arimoto et al. and there is no such teaching or suggestion in Painter et al. Arguable, the closest teaching or suggestion in Whitesides et al. refers to bacterial chemotaxis, but indicates that the mechanism of bacterial chemotaxis is "possibly non-polyvalent." This statement arguable teaches against use of polyvalent presenters for chemotaxis. Since there is no teaching or suggestion on the record that the mechanism of interaction of N-formyl peptides with neutrophils or any other cell is polyvalent or could be benefited by polyvalent presentation, one or ordinary skill in the art would not have been motivated to go to the significant effort to synthesize multivalent ligands containing N-formyl or N-acyl peptides. Further, there would be significant uncertainty that such multivalent ligands would retain biological

function in a multivalent form.

Because there is no motivation to make the combination suggested by the Office Action and further because there would be no reasonable expectation that the resulting multivalent ligands would retain function, this rejection should be withdrawn with respect to the claims as amended.

Claims 91 and 144 are further rejected under 35 U.S.C. 103(a) as being unpatentable over Whitesides et al., WO 98/46270 (reference 4, IDS filed 10/10/2002), Arimoto et al., Chem. Commun., July 1999, Vol. 15, 1361-1362, (IDS filed 10/10/2002, ref. 11) as applied to claims 1-3, 17, 18, 19, 20-23, 28-30, 41, 42, 59, 60, 62, 64, 68, 71- 74, 81, 82, 83, 90-92, 94, 95, 140-143, 144, 148, 149, 151, 154, 155, 157 above, and further in view of Truett, US 6,437,119 B1. Claim 144 no longer depends from claim 91 and has been amended to incorporate the limitation of claim 66 which is not rejected over this combination of references. This rejection should be withdrawn with respect to claim 144. Claim 91 now depends from amended claim 28 which carries the limitations of original claims 66 and 81. It is believed that the amendment of the claims obviates this rejection.

Neither Whitesides et al., Arimoto et al. nor Truett alone or in any combination teach or suggest the use of multivalent ligands carrying one or more N-formyl peptides or n-acyl peptides to induce secretion of an intracellular signal by a cell.

Claims 1-3, 17, 28, 29, 59, 60, 62, 64, 68, 71-74, 81, 82, 83, 90, 91, 142, 144, 152, 153 and 157 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kanai et al., J. Am. Chem. Soc, 1997, Vol. 119 (41), pp. 1361-1362, (IDS filed 10/10/2002, ref. 45) and Kaplan et al., J. Immunol. Methods 20: (1997) 15-24, (IDS filed 10/10/2002, reference 46).

Claims 1-3, 62 and 81 have been canceled. Claims 28 and 144 have been amended to incorporate the limitation of claim 66 which is not rejected over this combination of references. The remaining listed claims depend from claim 28. These amendments are believed to obviate the rejection.

Applicants note, however, that Kanai et al. relate only to the use of multivalent ligands carrying mannose residues for inhibition of Con A-promoted agglutination. Kanai et al. does not teach the use of multivalent ligands comprising Con A as is alleged in the reasoning supporting the rejection. No such teaching is found in the Kanai et al. reference. Kanai et al. relates to inhibition of Con A binding.

Allowable Claims

Claims 145-147 are considered allowable over the prior art. Applicants have amended these claims to depend from claim 144 which is believed as argued herein to be patentable over all of the prior art of record. Claim 144 is also not rejected under 35 U.S.C. 112, first paragraph. It is believed that all of claims 144, 141, 145-147 should be considered allowable.

Conclusion

Claim 28 has been amended to be independent and includes the additional limitation of original claims 66 and 81. Claim 28 also recites that the signal recognition element can be one or more N-acyl peptides. Claims 17, 20-23, 29, 30, 41-43, 59-61, 64, 66, 68, 71-74, 82-84, 90-92, 140, 142, 143, 148, 151-155, 157 and 162-164 all depend from claim 28 as amended.

Claim 144 has been made independent and includes the additional limitation of original claim 66. Claims 141, 145-147 and new claim 158 now depend from claim 144.

New claim 159 is similar in scope to amended claim 144 as discussed above and is presented as an independent claim. New claims 160 and 161 depend from claim 159.

The amendment of the claims obviates the rejection of all of the claims remaining in this case under 35 U.S.C. 102.

The amendment of the claims is also believed to obviate the rejections under 35 U.S.C. 103 over each of the combination of Whitesides et al. and Arimoto; the combination of Whitesides et al., Arimoto and Truett and the combination of Kanai et al. and Kaplan et al.

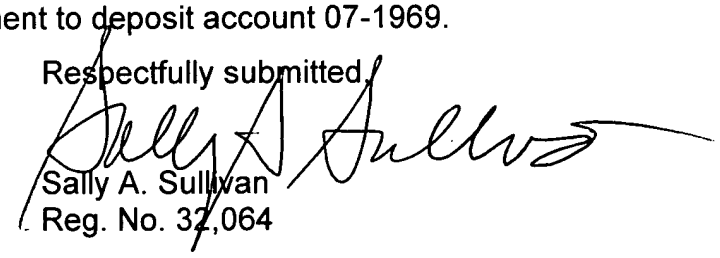
Applicants have presented arguments above that the claims as amended are patentable over the combination of Whitesides et al., Arimoto et al. and Painter.

Applicants have presented arguments that the claims as amended (claim 28 and its dependents) provide an adequate written description. Applicants note that claims 144-150 were not rejected for insufficient written description. It is believed that claim 159 which are similar in scope to claim 144 should also be considered to be sufficiently described.

It is believed that the claims as amended are patentable over the prior art cited and that the application meets the written description requirement with respect to the claims as amended.

This amendment cancels 113 claims and adds 7 claims. The claims contain a total of three independent claims. No fees for excess claims are believed to be due. This response is accompanied by a Petition for Extension of Time of Three Months with appropriate fee. A check in the amount of $510 accompanies this response. If the fees submitted are incorrect, please deduct any deficiency or credit any overpayment to deposit account 07-1969.

Respectfully submitted,



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